

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

Approval Package for:

APPLICATION NUMBER:

40-420

Generic Name: Phenytoin Oral Suspension USP,
125mg/5mL

Sponsor: Morton Grove Pharmaceuticals, Inc.

Approval Date: April 19, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-420

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**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

40-420

APPROVAL LETTER

ANDA 40-420

APR 19 2002

Morton Grove Pharmaceuticals, Inc.
Attention: Yogita Desai
6451 West Main Street
Morton Grove, IL 60053

Dear Madam:

This is in reference to your abbreviated new drug application dated September 29, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Phenytoin Oral Suspension USP, 125 mg/5 mL.

Reference is also made to your amendments dated July 11, July 20, 2001; and February 22, 2002.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Phenytoin Oral Suspension USP, 125 mg/5 mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Dilantin[®] Oral Suspension, 125 mg/5 mL, of Parke Davis, Division of Warner Lambert Co.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print.

Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,



Gary Buehler
Director

4/19/02

Office of Generic Drugs
Center for Drug Evaluation and Research

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

40-420

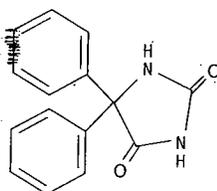
FINAL PRINTED LABELING

PHENYTOIN
ORAL SUSPENSION, USP
125 mg/5 mL
Rx only

APPROVED
APR 19 2002

DESCRIPTION

Phenytoin is related to the barbiturates in chemical structure, but has a five-membered ring. The chemical name is 5,5-diphenylhydantoin, having the following structural formula:



Each teaspoonful of suspension contains 125 mg of phenytoin, USP with an alcohol content of 0.35 percent. Also contains carboxymethylcellulose sodium, citric acid anhydrous, dehydrated alcohol, glycerin, liquid sugar, magnesium aluminum silicate, orange flavor, polysorbate 40, purified water, sodium benzoate, sodium citrate dihydrate, vanillin, and FD&C yellow No. 6. It may contain 10% sodium citrate solution or 10% citric acid solution to adjust pH.

CLINICAL PHARMACOLOGY

Phenytoin is an antiepileptic drug which can be useful in the treatment of epilepsy. The primary site of action appears to be the motor cortex where spread of seizure activity is inhibited. Possibly by promoting sodium efflux from neurons, phenytoin tends to stabilize the threshold against hyperexcitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient. This includes the reduction of posttetanic potentiation at synapses. Loss of posttetanic potentiation prevents cortical seizure foci from detonating adjacent cortical areas. Phenytoin reduces the maximal activity of brain stem centers responsible for the tonic phase of tonic-clonic (grand mal) seizures.

The plasma half-life in man after oral administration of phenytoin averages 22 hours, with a range of 7 to 42 hours. Steady-state therapeutic levels are achieved at least 7 to 10 days (5-7 half-lives) after initiation of therapy with recommended doses of 300 mg/day.

When serum level determinations are necessary, they should be obtained at least 5-7 half-lives after treatment initiation, dosage change, or addition or subtraction of another drug to the regimen so that equilibrium or steady-state will have been achieved. Trough levels provide information about clinically effective serum level range and confirm patient compliance and are obtained just prior to the patient's next scheduled dose. Peak levels indicate an individual's threshold for emergence of dose-related side effects and are obtained at the time of expected peak concentration. For Phenytoin Oral Suspension peak levels occur 1½-3 hours after administration.

Optimum control without clinical signs of toxicity occurs more often with serum levels between 10 and 20 mcg/mL, although some mild cases of tonic-clonic (grand mal) epilepsy may be controlled with lower serum levels of phenytoin.

In most patients maintained at a steady dosage, stable phenytoin serum levels are achieved. There may be wide interpatient variability in phenytoin serum levels with equivalent dosages. Patients with unusually low levels may be noncompliant or hypermetabolizers of phenytoin. Unusually high levels result from liver disease, congenital enzyme deficiency, or drug interactions which result in metabolic interference. The patient with large variations in phenytoin plasma levels, despite standard doses, presents a difficult clinical problem. Serum level determinations in such patients may be particularly helpful. As phenytoin is highly protein bound, free phenytoin levels may be altered in patients whose protein binding characteristics differ from normal.

Most of the drug is excreted in the bile as inactive metabolites which are then reabsorbed from the

intestinal tract and excreted in the urine. Urinary excretion of phenytoin and its metabolites occurs partly with glomerular filtration but more importantly, by tubular secretion. Because phenytoin is hydroxylated in the liver by an enzyme system which is saturable at high plasma levels small incremental doses may increase the half-life and produce very substantial increases in serum levels, when these are in the upper range. The steady-state level may be disproportionately increased, with resultant intoxication, from an increase in dosage of 10% or more.

INDICATIONS AND USAGE

Phenytoin Oral Suspension is indicated for the control of tonic-clonic (grand mal) and psychomotor (temporal lobe) seizures.

Phenytoin serum level determinations may be necessary for optimal dosage adjustments (see **DOSAGE AND ADMINISTRATION** and **CLINICAL PHARMACOLOGY** sections).

CONTRAINDICATIONS

Phenytoin Oral Suspension is contraindicated in those patients with a history of hypersensitivity to phenytoin or other hydantoin.

WARNINGS

Abrupt withdrawal of phenytoin in epileptic patients may precipitate status epilepticus. When in the judgment of the clinician the need for dosage reduction, discontinuation, or substitution of alternative anticonvulsant medication arises, this should be done gradually. In the event of an allergic or hypersensitivity reaction, more rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an anticonvulsant not belonging to the hydantoin chemical class.

There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalized) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's Disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling serum sickness e.g., fever, rash, and liver involvement.

In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative antiepileptic drugs.

Acute alcoholic intake may increase phenytoin serum levels while chronic alcoholic use may decrease serum levels.

In view of isolated reports associating phenytoin with exacerbation of porphyria, caution should be exercised in using this medication in patients suffering from this disease.

Usage in Pregnancy: A number of reports suggests an association between the use of antiepileptic drugs by women with epilepsy and a higher incidence of birth defects in children born to these women. Data are more extensive with respect to phenytoin and phenobarbital, but these are also the most commonly prescribed antiepileptic drugs; less systematic or anecdotal reports suggest a possible similar association with the use of all known antiepileptic drugs.

The reports suggesting a higher incidence of birth defects in children of drug-treated epileptic women cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodologic problems in obtaining adequate data on drug teratogenicity in humans; genetic factors or the epileptic condition itself may be more important than drug therapy in leading to birth defects. The great majority of mothers on antiepileptic medication deliver normal infants. It is important to note that antiepileptic drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazards to the developing embryo or fetus. The prescribing physician will wish to weigh these considerations in treating and counseling epileptic women of childbearing potential.

In addition to the reports of increased incidence of congenital malformation, such as cleft lip/palate and heart malformations in children of women receiving phenytoin and other antiepileptic drugs, there have more recently been reports of a fetal hydantoin syndrome. This consists of prenatal growth deficiency, microcephaly and mental deficiency in children born to mothers who have received phenytoin, barbiturates, alcohol, or trimethadione. However, these features are all interrelated and are frequently associated with intrauterine growth retardation from other causes.

There have been isolated reports of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy.

An increase in seizure frequency during pregnancy occurs in a high proportion of patients, because of altered phenytoin absorption or metabolism. Periodic measurement of serum phenytoin levels is particularly valuable in the management of a pregnant epileptic patient as a guide to an appropriate adjustment of dosage. However, postpartum restoration of the original dosage will probably be indicated.

Neonatal coagulation defects have been reported within the first 24 hours in babies born to epileptic mothers receiving phenobarbital and/or phenytoin. Vitamin K has been shown to prevent or correct this defect and has been recommended to be given to the mother before delivery and the neonate after birth.

PRECAUTIONS

General: The liver is the chief site of biotransformation of phenytoin; patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity.

A small percentage of individuals who have been treated with phenytoin have been shown to metabolize the drug slowly. Slow metabolism may be due to limited enzyme availability and lack of induction; it appears to be genetically determined.

Phenytoin should be discontinued if a skin rash appears (see **WARNINGS** section regarding drug discontinuation). If the rash is exfoliative, purpuric, or bullous or if lupus erythematosus, Stevens-

Johnson syndrome, or toxic epidermal necrolysis is suspected, use of this drug should not be resumed and alternative therapy should be considered (see **ADVERSE REACTIONS** section). If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further phenytoin medication is contraindicated. Phenytoin and other hydantoin are contraindicated in patients who have experienced phenytoin hypersensitivity. Additionally, caution should be exercised if using structurally similar (e.g., barbiturates, succinamides, oxazolindiones and other related compounds) in these same patients. Hyperglycemia, resulting from the drug's inhibitory effects on insulin release, has been reported. Phenytoin may also raise the serum glucose level in diabetic patients.

Osteomalacia has been associated with phenytoin therapy and is considered to be due to phenytoin's interference with Vitamin D metabolism.

Phenytoin is not indicated for seizures due to hypoglycemic or other metabolic causes. Appropriate diagnostic procedures should be performed as indicated.

Phenytoin is not effective for absence (petit mal) seizures. If tonic-clonic (grand mal) and absence (petit mal) seizures are present, combined drug therapy is needed.

Serum levels of phenytoin sustained above the optimal range may produce confusional states referred to as "delirium," "psychosis," or "encephalopathy," or rarely irreversible cerebellar dysfunction. Accordingly, at the first sign of acute toxicity, plasma levels are recommended. Dose reduction of phenytoin therapy is indicated if plasma levels are excessive; if symptoms persist, termination is recommended (see **WARNINGS** section).

Information for Patients: Patients taking phenytoin should be advised of the importance of adhering strictly to the prescribed dosage regimen, and of informing the physician of any clinical condition in which it is not possible to take the drug orally as prescribed, e.g., surgery, etc.

Patients should be instructed to use an accurately calibrated measuring device when using this medication to ensure accurate dosing.

Patients should also be cautioned on the use of other drugs or alcoholic beverages without first seeking the physician's advice.

Patients should be instructed to call their physician if skin rash develops.

The importance of good dental hygiene should be stressed in order to minimize the development of gingival hyperplasia and its complications.

Laboratory Tests: Phenytoin serum level determinations may be necessary to achieve optimal dosage adjustments.

Drug Interactions: There are many drugs which may increase or decrease phenytoin levels or which phenytoin may affect. Serum level determinations for phenytoin are especially helpful when possible drug interactions are suspected. The most commonly occurring drug interactions are:

1. Drugs which may increase phenytoin serum levels include: acute alcohol intake, amiodarone, chloramphenicol, chlorthalidone, diazepam, dicumarol, disulfiram, estrogens, ethosuximide, H₂-antagonists, halothane, isoniazid, methylphenidate, phenothiazines, phenylbutazone, salicylates, succinimides, sulfonamides, tolbutamide, trazodone.

2. Drugs which may decrease phenytoin levels include: carbamazepine, chronic alcohol abuse, reserpine, and sucralofate. Moban® brand of molindone hydrochloride contains calcium ions which interfere with the absorption of phenytoin. Ingestion times of phenytoin and antacid preparations containing calcium should be staggered in patients with low serum phenytoin levels to prevent absorption problems.

3. Drugs which may either increase or decrease phenytoin serum levels include: phenobarbital, sodium valproate, and valproic acid. Similarly, the effect of phenytoin on phenobarbital, valproic acid, and sodium valproate serum levels is unpredictable.

4. Although not a true drug interaction, tricyclic antidepressants may precipitate seizures in susceptible patients and phenytoin dosage may need to be adjusted.

5. Drugs whose efficacy is impaired by phenytoin include: corticosteroids, coumarin anticoagulants, digitoxin, doxycycline, estrogens, furosemide, oral contraceptives, quinidine, rifampin, theophylline, vitamin D.

Drug/Laboratory Test Interactions: Phenytoin may cause decreased serum levels of protein-bound iodine (PBI). It may also produce lower than normal values for dexamethasone or metyrapone tests. Phenytoin may cause increased serum levels of glucose, alkaline phosphatase, and gamma glutamyl transpeptidase (GGT).

Carcinogenesis: See **WARNINGS** section for information on carcinogenesis.

Pregnancy: See **WARNINGS** section.

Nursing Mothers: Infant breast feeding is not recommended for women taking this drug because phenytoin appears to be secreted in low concentrations in human milk.

Pediatric Use: See **DOSAGE AND ADMINISTRATION** section.

ADVERSE REACTIONS

Central Nervous System: The most common manifestations encountered with phenytoin therapy are referable to this system and are usually dose-related. These include nystagmus, ataxia, slurred speech, decreased coordination, and mental confusion. Dizziness, insomnia, transient nervousness, motor twitchings, and headaches have also been observed. There have also been rare reports of phenytoin induced dyskinesias, including chorea, dystonia, tremor and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs.

A predominantly sensory peripheral polyneuropathy has been observed in patients receiving long-term phenytoin therapy.

Gastrointestinal System: Nausea, vomiting, constipation, toxic hepatitis and liver damage.

Integumentary System: Dermatological manifestations sometimes accompanied by fever have included scarlatiniform or morbilliform rashes. A morbilliform rash (measles-like) is the most common; other types of dermatitis are seen more rarely. Other more serious forms which may be fatal have included bullous, exfoliative or purpuric dermatitis, lupus erythematosus, Stevens-

Johnson syndrome, and toxic epidermal necrolysis (see **PRECAUTIONS** section).

Hemopoietic System: Hemopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression. While macrocytosis and megaloblastic anemia have occurred, these conditions usually respond to folic acid therapy. Lymphadenopathy including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's Disease have been reported (see **WARNINGS** section).

Connective Tissue System: Coarsening of the facial features, enlargement of the lips, gingival hyperplasia, hypertrichosis, and Peyronie's disease.

Cardiovascular: Periarteritis nodosa.

Immunologic: Hypersensitivity syndrome (which may include, but is not limited to, symptoms such as arthralgias, eosinophilia, fever, liver dysfunction, lymphadenopathy or rash), systemic lupus erythematosus, and immunoglobulin abnormalities.

OVERDOSAGE

The lethal dose in pediatric patients is not known. The lethal dose in adults is estimated to be 2 to 5 grams. The initial symptoms are nystagmus, ataxia, and dysarthria. Other signs are tremor, hyperreflexia, lethargy, slurred speech, nausea, vomiting. The patient may become comatose and hypotensive. Death is due to respiratory and circulatory depression.

There are marked variations among individuals with respect to phenytoin plasma levels where toxicity may occur. Nystagmus, on lateral gaze, usually appears at 20 mcg/mL, ataxia at 30 mcg/mL, dysarthria and lethargy appear when the plasma concentration is over 40 mcg/mL, but as high a concentration as 50 mcg/mL has been reported without evidence of toxicity. As much as 25 times the therapeutic dose has been taken to result in a serum concentration over 100 mcg/mL with complete recovery.

Treatment: Treatment is nonspecific since there is no known antidote.

The adequacy of the respiratory and circulatory systems should be carefully observed and appropriate supportive measures employed. Hemodialysis can be considered since phenytoin is not completely bound to plasma proteins. Total exchange transfusion has been used in the treatment of severe intoxication in pediatric patients.

In acute overdosage the possibility of other CNS depressants, including alcohol, should be borne in mind.

DOSAGE AND ADMINISTRATION

Serum concentrations should be monitored and care should be taken when switching a patient from the sodium salt to the free acid form. The free acid form of phenytoin is used in Phenytoin Oral Suspension. Because there is approximately an 8% increase in drug content with the free acid form over that of the sodium salt, dosage adjustments and serum level monitoring may be necessary when switching from a product formulated with the free acid to a product formulated with the sodium salt and vice versa.

General: Dosage should be individualized to provide maximum benefit. In some cases serum blood level determinations may be necessary for optimal dosage adjustments—the clinically effective serum level is usually 10-20 mcg/mL. With recommended dosage, a period of seven to ten days may be required to achieve steady-state blood levels with phenytoin and changes in dosage (increase or decrease) should not be carried out at intervals shorter than seven to ten days.

Adult Dose: Patients who have received no previous treatment may be started on one teaspoonful (5 mL) of Phenytoin Oral Suspension three times daily, and the dose is then adjusted to suit individual requirements. An increase to five teaspoonfuls daily may be made, if necessary.

Pediatric Dose: Initially, 5 mg/kg/day in two or three equally divided doses, with subsequent dosage individualized to a maximum of 300 mg daily. A recommended daily maintenance dosage is usually 4 to 8 mg/kg. Children over 6 years and adolescents may require the minimum adult dose (300 mg/day).

HOW SUPPLIED

Phenytoin Oral Suspension, USP 125 mg phenytoin/5 mL with an alcohol content of 0.35 percent, an orange suspension with an orange-vanilla flavor; available in 237 mL (8 fl oz) bottles.

Store at controlled room temperature, 15°-30° C (59°-86° F) [see USP]. Protect from freezing and light.

Rx Only

Prod. No.: 8131

Manufactured By:
Morton Grove Pharmaceuticals, Inc.
Morton Grove, IL 60053

28131
ISS. 6-01

3 60432-131-08 7



THIS PRODUCT MUST BE SHAKEN WELL ESPECIALLY PRIOR TO INITIAL USE.
Each 5 mL (teaspoonful) contains Phenytoin, 125 mg with an alcohol content of 0.35 percent.
USUAL DOSAGE—Adults, 1 teaspoonful (5 mL) three times daily; pediatric patients, see package insert.

MGP	NDC 60432-131-08
	PHENYTOIN ORAL SUSPENSION, USP
125 mg/5 mL	(Contains alcohol 0.35 percent)
IMPORTANT — SHAKE WELL BEFORE EACH USE	
DO NOT USE IF BAND PRINTED "SEALED FOR YOUR PROTECTION" AROUND CAP IS BROKEN OR MISSING.	
Rx Only	
NET: 237 mL (8 fl oz)	

Advice to Pharmacist and Patient —
Patient must be advised to use an accurate measuring device when using this product.

See package insert for complete prescribing information.

Store at controlled room temperature, 15°-30°C (59°-86°F) [see USP].

WARNING: KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Protect from freezing.

Protect from light.

Manufactured By:
Morton Grove Pharmaceuticals, Inc.
Morton Grove, IL 60053

50-8131-08
ISS. 6-01

AP 4/13/02
420-420

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

40-420

CHEMISTRY REVIEW(S)

ANDA APPROVAL SUMMARY

AADA: 40-420

DRUG PRODUCT: Phenytoin Oral Suspension, USP

FIRM: Morton Grove Pharmaceuticals, Inc.

DOSAGE FORM: Oral Suspension, USP

STRENGTH: 125 mg/5 mL

CGMP STATEMENT/EIR UPDATE STATUS: Signed cGMP certifications provided on pages 2127 in original application. EER is withhold dated 10/22/01.

BIO STUDY: The bio-study conducted on the applicant's products (125 mg/5 ml) and Dilantin-125[®] were found acceptable by the Division of Bioequivalence on 7/26/01.

METHOD VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): The drug substance and Drug product are both USP.

STABILITY - (ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?): Accelerated and room temperature stability data support the proposed 24 month expiration date. Containers used in the stability studies were identical to those described in the container section.

LABELING: Satisfactory as of 9/14/01

STERILIZATION VALIDATION (IF APPLICABLE): Not-applicable to this drug product.

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?): Exhibit batch (# A0253) used for stability and bio-studies were manufactured with bulk drug substance from ~~_____~~
The size for batch (# A0253) is ~~_____~~

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?): See above

PROPOSED PRODUCTION BATCH - (MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?): The proposed production batch size is ~~_____~~
~~_____~~ The manufacturing process described in the master production records is same as that described in the exhibit batch record.

1. CHEMISTRY REVIEW NO. 1
2. ANDA # 40420
3. NAME AND ADDRESS OF APPLICANT
Morton Grove Pharmaceuticals, Inc.
6451 West Main Street
Morton Grove, IL 60053
4. LEGAL BASIS FOR SUBMISSION
Innovator Product: Dilantin-125
Innovator Company: Parke-Davis Division of Warner-Lambert
Patent Expiration Date: No unexpired patents or exclusivity for this drug product.
5. SUPPLEMENT(s)
N/A
6. PROPRIETARY NAME
N/A
7. NONPROPRIETARY NAME
Phenytoin Oral Suspension, USP 125 mg/5 mL
8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A
9. AMENDMENTS AND OTHER DATES:

Submission date	Submission type
09/29/00	Original
2/2/01	Amendment

10. PHARMACOLOGICAL CATEGORY
Anticonvulsant
11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

DMF number	DMF type	LOA(s) (page)
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	III	
	IV	
	III	
	III	
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	III	

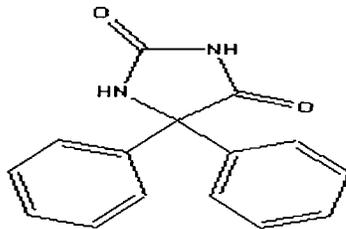
13. DOSAGE FORM
Suspension

14. POTENCY

Strength
125 mg/5 m

15. CHEMICAL NAME AND STRUCTURE

CAS number: 57-41-0
Molecular Weight: 252.27
Chemical Name: 2,4-Imidazolidinedione,
5,5-diphenyl-5,5-
diphenylhydantoin



Structure:

16. RECORDS AND REPORTS
N/A

17. COMMENTS

[]

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approvable (MINOR)

19. REVIEWER:
Yanping Pan

DATE COMPLETED:
4/13/01

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Page(s) of trade

secret and /or

confidential

commercial

information

1. CHEMISTRY REVIEW NO. 2
2. ANDA # 40420
3. NAME AND ADDRESS OF APPLICANT
Morton Grove Pharmaceuticals, Inc.
6451 West Main Street
Morton Grove, IL 60053
4. LEGAL BASIS FOR SUBMISSION
Innovator Product: Dilantin-125
Innovator Company: Parke-Davis Division of Warner-Lambert
Patent Expiration Date: No unexpired patents or exclusivity for this drug product.
5. SUPPLEMENT(s)
N/A
6. PROPRIETARY NAME
N/A
7. NONPROPRIETARY NAME
Phenytoin Oral Suspension, USP 125 mg/5 mL
8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A
9. AMENDMENTS AND OTHER DATES:

Submission date	Submission type
09/29/00	Original
2/2/01	Amendment
9/20/01	Minor Amendment

10. PHARMACOLOGICAL CATEGORY
Anticonvulsant
11. Rx or OTC
Rx
12. RELATED IND/NDA/DMF(s)

**APPEARS THIS WAY
ON ORIGINAL**

DMF number	DMF type	LOA(s) (page)
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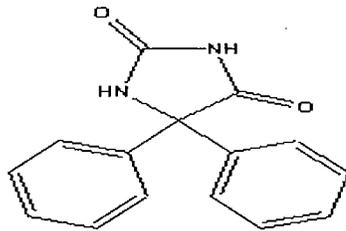
13. DOSAGE FORM
Suspension

14. POTENCY

Strength
125 mg/5 mL

15. CHEMICAL NAME AND STRUCTURE

CAS number: 57-41-0
Molecular Weight: 252.27
Chemical Name: 2,4-Imidazolidinedione,
5,5-diphenyl-5,5-diphenylhydantoin



Structure:

16. RECORDS AND REPORTS

N/A

17. COMMENTS

[]

This review covers Amendment September 20, 2001

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Page(s) of trade

secret and /or

confidential

commercial

information

1. CHEMISTRY REVIEW NO. 3
2. ANDA # 40420
3. NAME AND ADDRESS OF APPLICANT
Morton Grove Pharmaceuticals, Inc.
6451 West Main Street
Morton Grove, IL 60053
4. LEGAL BASIS FOR SUBMISSION
Innovator Product: Dilantin-125
Innovator Company: Parke-Davis Division of Warner-Lambert
Patent Expiration Date: No unexpired patents or exclusivity for this drug product.
5. SUPPLEMENT(s)
N/A
6. PROPRIETARY NAME
N/A
7. NONPROPRIETARY NAME
Phenytoin Oral Suspension, USP 125 mg/5 mL
8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A
9. AMENDMENTS AND OTHER DATES:

<u>Submission date</u>	<u>Submission type</u>
09/29/00	Original
2/2/01	Amendment
9/20/01	Minor Amendment
2/22/02	Minor Amendment

10. PHARMACOLOGICAL CATEGORY
Anticonvulsant
11. Rx or OTC
Rx
12. RELATED IND/NDA/DMF(s)

**APPEARS THIS WAY
ON ORIGINAL**

DMF number	DMF type	LOA(s) (page)
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	III	
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	IV	
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	III	
	II	
	III	
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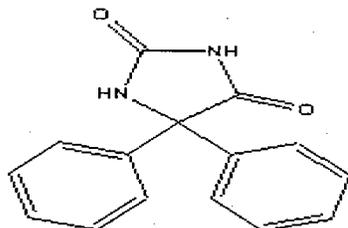
13. DOSAGE FORM
Suspension

14. POTENCY

Strength
125 mg/5 mL

15. CHEMICAL NAME AND STRUCTURE

CAS number: 57-41-0
Molecular Weight: 252.27
Chemical Name: 2,4-Imidazolidinedione,
5,5-diphenyl-5,5-diphenylhydantoin



Structure:

16. RECORDS AND REPORTS
N/A

17. COMMENTS

EERs: **withhold (10/22/01)**
DMF (# —, status: adequate (2/20/01)
Labeling review: Approved (9/14/01)
Bio-review: Acceptable (7/26/01)
Micro review: N/A

This review covers Minor Amendment dated 2/22/02

#1 deficiency per review 2:

The specific gravity limit for finished product is not same as that for stability study. Please provide justification.

Response:

Based on the accrued stability data, MGP has revised the limits for specific gravity for the stability study to be consistent with limits for finished product. The limits have been tightened from to

Comment per CR#3:

It is satisfactory.

#2 deficiency per review 2:

Please tighten your Sodium Benzoate specification for stability study.

Response:

Based on the discussion with OGD reviewer, the specification for Sodium Benzoate as currently established is acceptable to the FDA.

Comment Per CR#3:

It is satisfactory.

#3 deficiency per review 2:

We noticed that the following specifications listed in your Finished Product Quality Control Test Record and in your Certificate of Analysis are not consistent. Please clarify.

- *Sodium Benzoate*
- *Viscosity*
- *pH*
- *Specific gravity*
- *Individual known, individual unknown and total impurities*
- *Microbial limits*

Response:

MGP's Finished Product Quality Control Test Record (MGP Form 167) is the official document for released or rejected finished product. The Certificate of Analysis (MGP form 166) is a summary sheet prepared for MGP's customers and is shipped with the product. Thus, MGP Form 167 states release specifications, while MGP Form 166 summarizes stability specifications (per MGP Form 163). All tests included in Form 167 are included on Form 166 except for assay for degradants/impurities (individual and total).

Comment per CR#3:

It is satisfactory.

#4 deficiency per review 2:

We continue believing that you should tighten specifications for individual known and individual unknown impurities in your release and during stability for the drug product to reflect your actual data.

Response:

The limits for individual known and unknown impurities in the stability of the drug product have been tightened and revised as follows:

Parameters	Stability specification	
	From	To
Degradant/impurities individual (known)	NMT —	NMT —
Degradant/impurities individual (unknown)	NMT —	NMT —

Comment per CR#3:

The revised limits for individual known and unknown impurities in release and the stability of the drug product are as follows:

Parameters	Release specification	Stability specification
Degradant/impurities individual (known)	NMT —	NMT —
Degradant/impurities individual (unknown)	NMT —	NMT —

For total impurity specification, please see #6 deficiency. It is acceptable.

#5 deficiency per review 2:

We noticed that you deleted Antimicrobial Effectiveness testing and Microbial Limits testing from finished product quality control test. Please clarify.

Response:

MGP has not decreased the microbial testing commitments for this product.

MGP submits that the Microbial Limit testing continues to be reported without any changes as indicated on page 9 of 9 of MGP Form 167, finished Product Quality Control Test Record (Attachment 3).

The Antimicrobial Effectiveness Testing has been the subject of Minor reporting changes. The Antimicrobial Effectiveness Testing will be reported on MGP Form 165, Antimicrobial Effectiveness Test Worksheet (Attachment 5), which is a batch record document.

Comment per CR#3:

It is satisfactory.

#6 deficiency per review 2:

Please tighten the following limits during stability study for your drug product to reflect actual data:

- pH
- Total impurity

Response:

The Limit for pH in the stability of the drug product has been tightened and revised from " _____ " to " _____ " .

The limits for total impurity in the release and stability of the drug product have been tightened and revised as follows:

Parameters	Release specification		Stability specification	
	From	To	From	To
Total impurities	NMT _____	NMT _____	NMT _____	NMT _____

Comment per CR#3:

It is satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS

Approval (Pending Satisfactory EER)

19. REVIEWER:

Yanping Pan

DATE COMPLETED:

3/7/02

**APPEARS THIS WAY
ON ORIGINAL**

Redacted 15

Page(s) of trade

secret and /or

confidential

commercial

information

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

40-420

**BIOEQUIVALENCE
REVIEW(S)**

Phenytoin Oral Suspension
125 mg/5 ml
ANDA #40-420
Reviewer: J. Lee
40420STA.701

Morton Grove Pharmaceuticals, Inc.
Morton Grove, Illinois
Submission date:
July 20, 2001

Review of a Study Amendment

This amendment is a response to the deficiencies issued in the review of the bio-study contained in the original submission (Sept 29, 2000).

1. The complete analytical methodology including the preparation of standards and quality control samples, description of instrumentation parameters, sample and standard processing procedure, etc. were not included in the bio-study report. This information plus the analytical SOPs were requested.
☞ The requested information was submitted. (**Not to be Released Under FOI**) The method entailed processing samples using ~~Stability~~ Stability and recovery information which were only available electronically in the original submission were included in this amendment.
2. The potency of the reference drug used in the bio-study was not reported. The sponsor was asked to supply the potency of Dilantin-125[®], batch #39839L.
☞ The potency of Dilantin-125[®], batch #39839L, was stated to be 99.2%.
3. Since the USP dissolution method had changed after receiving the original submission, the sponsor was requested to redo the dissolution testing per USP 24, suppl 3 (the latest supplement), using the same batches of test/reference products employed in the bio-study. The sponsor has also attested that the dissolution method in USP 24, suppl 3, will now be their current in-house method.

Additionally, since the reference drug used in the bio-study had expired, the sponsor was requested to conduct dissolution testing on a fresh reference batch. Potency was also requested to be determined for the fresh reference batch.

- ☞ See attachments for the dissolution summaries. The potency for the fresh reference batch was 99.1% (batch # 64090L - expiry date: 8/2002). Content uniformity was also determined:

Dilantin-125 [®] , batch #39839L (bio-batch)	101.3%
Dilantin-125 [®] , batch #64090L (fresh ref batch)	101.1%
Morton Grove, batch #A0253 (bio-batch)	100.5%

Comment:

1. The USP 24, suppl 3 dissolution method for phenytoin oral suspension specifies a sampling time (60 min), but not a Q. DBE is applying a Q = — in 60 minutes as an interim specification until such time as the USP issues a Q for the dissolution method.
2. All deficiencies have been satisfactorily addressed.

Recommendation:

1. The bioequivalence study conducted by _____ for Morton Grove Pharmaceuticals, Inc. on its phenytoin 125 mg/5 ml oral suspension, batch #A0253, comparing it to Dilantin-125®, has been found acceptable to the Division of Bioequivalence.
2. The in-vitro dissolution testing data is also acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of 0.05M tris buffer at 37°C using USP XXIV apparatus II (paddle) at 35 rpm. The test product should meet the following specification:

Not less than — of the labeled amount of the drug in the suspension is dissolved in 60 minutes.

3. All bioequivalence criteria have been met.

J. Lee 7/26/01

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

[Signature]

7/26/2001

Concur: *[Signature]* Date: *7/30/01*

Dale Conner, Pharm. D.
Director, Division of Bioequivalence

JLee/jl/07-26-01

cc: NDA #40-420 (original, duplicate), HFD-630, HFD-655 (Lee, Patnaik), Drug File, Division File

Method Ref.:	USP 24, suppl 3	Medium:	0.05M tris buffer
USP 24 Apparatus:	II	Volume:	900 mL
RPM:	35	Tolerance:	Q= - % in 60 min
No. Units Tested:	12		(interim)
Reference Drug:	Dilantin-125®	Assay Method:	_____

Sampling Times (Minutes)	Test Product: Lot No.: A0253 (glass ctn) (bio-batch) Strength: 125 mg/5ml			Ref Product: Lot No.: 39839L (glass ctn) (bio-batch) Strength: 125 mg/5ml		
	Mean (%)	Range	% CV	Mean (%)	Range	% CV
10	15.6	[]	16	24.6	[]	27
20	48.5		13	64.6		11
30	80.3		8.4	89		4.7
45	98.5		2.4	100		2.4
60	101.4		0.7	101.7		2.9
90	101.8		0.7	102.3		2.9

f₂ = 53.76

Sampling Times (Minutes)	Test Product: Lot No.: A0253 (PET ctn) Strength: 125 mg/5ml			Ref Product: Lot No.: 64090L (glass ctn) (new ref batch) Strength: 125 mg/5ml		
	Mean (%)	Range	% CV	Mean (%)	Range	% CV
10	25.6	[]	20	24.1	[]	8.7
20	64.3		10	52.2		5.5
30	89.6		4.4	72.6		4.6
45	100.9		1.9	89.3		3.7
60	102.5		1.7	97.4		2.1
90	102.5		1.9	101.7		0.6

f₂ = 49.91

CC: ANDA 40-420
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ Reviewer

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Endorsements: (Final with Dates)
HFD-655/ JLee *e.p. 7/26/01*
HFD-655/ Bio team Leader
HFD-650/ D. Conner *DB 7/30/01*

DB 7/26/01

BIOEQUIVALENCY - ACCEPTABLE

submission date: July 20, 2001

5. STUDY AMENDMENT (STA)

Strengths: 125 mg/5 ml
Outcome: AC

Outcome Decisions: AC - Acceptable

WinBio Comments:

All deficiencies satisfactorily addressed. Bio-study is acceptable.

**APPEARS THIS WAY
ON ORIGINAL**

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-420 APPLICANT: Morton Grove Pharmaceuticals, Inc.

DRUG PRODUCT: Phenytoin Oral Suspension USP, 125 mg/5 ml

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 24, suppl 3.

Please employ a Q of NLT \sim in 60 minutes as an interim specification until such time as the USP issues a Q for the dissolution method.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 40-420
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ Reviewer

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Printed in final on / /

Endorsements: (Final with Dates)

HFD-655/ JLee *J. 7/26/01*

HFD-655/ Bio team Leader

HFD-650/ D. Conner *DC 7/30/01*

[Signature] 7/26/01

BIOEQUIVALENCY - ACCEPTABLE

submission date: July 20, 2001

5. STUDY AMENDMENT (STA)

Strengths: 125 mg/5 ml

Outcome: AC

Outcome Decisions: AC - Acceptable

WinBio Comments:

All deficiencies satisfactorily addressed. Bio-study is acceptable.

**APPEARS THIS WAY
ON ORIGINAL**

**OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE**

ANDA #: 40-420

SPONSOR: Morton Grove Pharmaceuticals

DRUG AND DOSAGE FORM: Phenytoin oral suspension

STRENGTH(S): 125 mg/5ml

TYPES OF STUDIES: ~~fasted~~

CLINICAL STUDY SITE(S): _____

ANALYTICAL SITE(S): same

STUDY SUMMARY: bio study acceptable.

DISSOLUTION: OK per USP 34, suppl 3

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status:	Inspection results:
First Generic <u>NO</u>	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
other _____		

PRIMARY REVIEWER: J. Lee

BRANCH: II

INITIAL: L.J.

DATE: 7/26/01

TEAM LEADER: SG Nerurkar

BRANCH: II

INITIAL: [Signature]

DATE: 7/26/2001

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm. D.

INITIAL: DK

DATE: 7/30/01

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 40-420 APPLICANT: Morton Grove Pharmaceuticals, Inc.

DRUG PRODUCT: Phenytoin Oral Suspension USP, 125 mg/5 ml

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified.

1. You have not submitted the complete analytical methodology. The method should include the the preparation of standards and quality control samples, description of instrumentation parameters, sample and standard processing procedure, etc. This information may be found in analytical SOP # LMS-M-5972-01. Please also submit SOP # AL-G-1520-09 and AL-G-1520-09.A01 [Reporting of data generated by the Analytical Laboratories].
2. The potency of the reference drug used in the bio-study was not reported. Please supply the potency of Dilantin-125[®], batch #39839L.
3. Since the USP dissolution method has changed after receiving your submission, please redo the dissolution testing per USP 24, suppl 3, using the same batches of test/reference products employed in the bio-study.

900 ml of 0.05M Tris buffer
Apparatus II (paddle) @ 35 rpm
Sampling time: 10, 20 30, 45 and 60 minutes

In addition, since the reference drug used in the bio-study has expired, please conduct dissolution testing on a fresh reference batch. Potency should also be determined for the fresh reference batch.

Twelve dosage units of both test/reference products should be employed in all dissolution testing.

Sincerely yours,

fr 

Dale P. Conner, Pharm.D.
Director Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Phenytoin Oral Suspension
125 mg/5 ml
ANDA #40-420
Reviewer: J. Lee
40420S.S00

Morton Grove Pharmaceuticals, Inc.
Morton Grove, Illinois
Submission date:
September 29, 2000

Review of a Bioequivalence Study
(Electronic Submission)

Introduction

Indication: For the control of tonic-clonic (grand mal) and psychomotor (temporal lobe) seizures.

Type of Submission: ANDA

Contents of Submission: Fasted bio-study

RLD: Dilantin®-125 Suspension

Recommended Dose: Adults – one ts t.i.d. to start; dosage should be individualized.

Protocol No.: 980090, Comparative, Single-Dose, Fully-Replicated, 4-Period Crossover Bioavailability Study of Morton Grove and Parke-Davis (Dilantin-125(r)) 125 mg Phenytoin/5 mL Phenytoin Oral Suspension in Healthy Adult Males Under Fasting Conditions

Study Information

STUDY FACILITY INFORMATION

Clinical Facility: _____

Medical Director: _____

Scientific Director: _____

Clinical Study Dates: 11/24/99 to 01/30/00

Analytical Facility: _____

Principal Investigator: _____

Analytical Study Dates: 02/01/00 to 03/03/00

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Phenytoin	Dilantin-125®
Manufacturer:	Morton Grove Pharmaceuticals, Inc.	Parke-Davis (Div. of Warner- Lambert Co.)
Manufacture Date:	N/A	N/A
Expiration Date:	08/16/01 (temporary)	Feb 01
ANDA Batch Size:	_____	N/A

Batch/Lot Number:	A0253	39839L
Potency:	101.6%	???????????
Strength:	125 per 5 mL	125 per 5 mL
Dosage Form:	suspension	suspension
Dose Administered:	125 per 5 mL	125 per 5 mL
Study Condition:	fasting	fasting
Length of Fasting:	OVERNIGHT	OVERNIGHT

<u>RANDOMIZATION</u>		<u>DESIGN</u>	
Randomized:	Y	Design Type:	crossover
No. of Sequences:	2	Replicated Treatment Design:	Y
No. of Periods:	4	Balanced:	Y
No. of Treatments:	2	Washout Period:	21 days

Patients were dosed on the mornings of Nov 24 and Dec 15, 1999 and Jan 5 and 26, 2000.

seq I ABBA subj #1, 3, 4, 7, 9, 10, 13, 14, 17, 18, 19, 20, 23, 25, 27

seq II BAAB subj #2, 5, 6, 8, 11, 12, 15, 16, 18, 21, 22, 24, 26, 28

<u>DOSING</u>		<u>SUBJECTS</u>	
Single or Multiple Dose:	single	IRB Approval:	Y
Steady State:	N	Informed Consent Obtained:	Y
Volume of Liquid Intake:	240 mL	No. of Subjects Enrolled:	28
Route of Administration:	oral	No. of Subjects Completing:	28
Dosing Interval:	hr	No. of Subjects Plasma Analyzed:	24
Number of Doses:	N/A	No. of Dropouts:	0
Loading Dose:	per 5 mL	Sex(es) Included:	male
Steady State Dose Time:	N/A	Healthy Volunteers Only:	Y
Length of Infusion:	N/A	No. of Adverse Events:	2

Dietary Restrictions: No alcohol- or xanthine-containing beverages and foods for the 24 hours before each dosing and throughout the period of sample collection. No grapefruit-containing beverages and foods for 7 days before dosing and throughout the entire study.

Activity Restrictions: Subjects remained ambulatory or seated upright for the first 4 hours following drug administration, except when prevented by adverse events. No strenuous activity during the housing period.

Drug Restrictions: No medication (including over-the-counter products) for the 7 days preceding the study. This prohibition did not include vitamins taken as nutritional supplements for non-therapeutic indications.

Blood Sampling: 7 ml was collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 12, 16, 24, 36, 48, 72 and 96 hours post-dose.

Study Results

1) Clinical

Adverse Events: 2 reported (trt B) that were possibly related to the study drug [sore throat, trembling (more than usual)]. Both were mild in nature.

Protocol Deviations:

Dropouts:

No Dropouts Reported

2) Analytical (Not to be Released Under FOI)

Pre-Study Assay Validation:

ANALYTE:

ASSAY METHOD:

MATRIX:

INTERNAL STANDARD:

SENSITIVITY:

STANDARD CURVE HIGHEST CONC.:

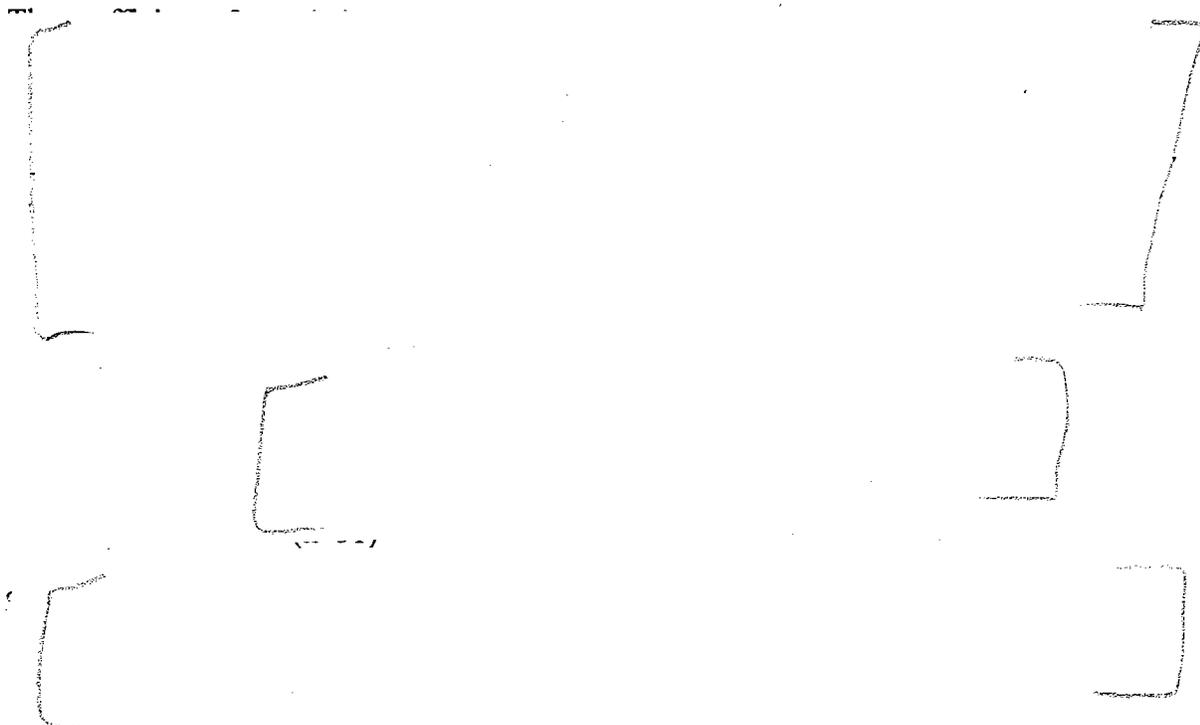
STANDARD CURVE LOWEST CONC.:

R² IS GREATER THAN:

SPECIFICITY:

ANALYTE RETENTION TIME:

INTERNAL STANDARD RETENTION TIME:



Recovery data showed the following:

3) Pharmacokinetic:

Plasma data was analyzed by an analysis of variance procedure to determine statistically significant ($p < 0.05$) differences between treatments, sequence of dosing, subjects within sequence and period for the pharmacokinetic parameters. All 28 subjects completed the study. The first 24 subjects were analyzed per protocol.

Results:

Results are given in the appended tables. There was $\leq 0.4\%$ difference between test and reference formulations in AUC_{0-t} and AUC_{inf} and a 15.5% difference in C_{max} . The 90% shortest confidence intervals for phenytoin are presented below. The DBE statistician verified the ANOVA of the replicate study.

	<u>90% CI</u> [log-transformed]
AUC_{0-t}	[97.3; 102.1]
AUC_{inf}	[97.0; 102.2]
C_{max}	[107.8; 123.6]

In-vitro Dissolution:

The sponsor has conducted dissolution testing with test/reference bio-lots used in this study, using the USP dissolution method in effect at the time of submission (USP 24, suppl 2). Since receiving the submission, the dissolution method has changed (USP 24, suppl3, eff. March 1, 2001). The sponsor will be requested to conduct dissolution testing using the current USP dissolution method.

Comment:

1. The sponsor has not submitted the complete analytical methodology. The method should include the preparation of standards and quality control samples, description of instrumentation parameters, sample and standard processing procedure, etc. This information may be found in analytical SOP # LMS-M-5972-01. The sponsor should

also submit SOP # AL-G-1520-09 and AL-G-1520-09.A01 [Reporting of data generated by the Analytical Laboratories].

2. The potency of the reference drug used in the bio-study was not reported. The sponsor should supply the potency of Dilantin-125®, batch #39839L.
3. The sponsor should redo the dissolution testing per USP 24, suppl 3, using the same batches of test/reference products employed in the bio-study.

900 ml of 0.05M Tris buffer
Apparatus II (paddle) @ 35 rpm
Sampling time: 10, 20 30, 45 and 60 minutes

In addition, since the reference drug used in the bio-study has expired, the sponsor should conduct dissolution testing on a fresh reference batch. Potency should also be determined for the fresh reference batch.

Twelve dosage units of both test/reference products should be employed in all dissolution testing.

Recommendation:

1. The bioequivalence study conducted by _____ for Morton Grove Pharmaceuticals Inc. on its phenytoin oral suspension, 125 mg/5ml, batch #A0253, has been found incomplete per comments #1-3.

J. Lee 5/17/01

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

[Signature]

6/8/2001

Concur: *[Signature]* Date: 6/14/2001

[Signature] Dale Conner, Pharm. D.
Director, Division of Bioequivalence

JLee/jl/05-17-01

cc: NDA #40-420 (original, duplicate), HFD-630, HFD-655 (Lee, Patnaik), Drug File, Division File

IN - VITRO DISSOLUTION TESTING

Method Ref.:	USP 24, suppl 2	Medium:	0.05 borate buffer			
USP 24 Apparatus:	II	Volume:	900 mL			
RPM:	50	Tolerance:	Q= — in 30 min.			
No. Units Tested:	see below: 5 ml ea	Assay Method:	—			
Reference Drug:	Dilantin®-125					
Sampling Times (Minutes)	Test Product: Lot No.: A0253 Strength: 125 mg/5 ml 12 units tested			Ref Product: Lot No.: 39839L Strength: 125 mg/5 ml 6 units tested		
	Mean (%)	Range	% CV	Mean (%)	Range	% CV
10	87.3	[]	7.7	84.6	[]	2.8
20	99.2	[]	3.3	95.2	[]	1.2
30	98.1	[]	3.2	97.3	[]	2.7
60	100.0	[]	3.5	96.3	[]	1.3

**APPEARS THIS WAY
ON ORIGINAL**

FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #980090
 ARITHMETIC MEAN PLASMA CONCENTRATIONS [NG/ML] (CV%)
 VERSUS TIME IN 24 SUBJECTS
 PHENYTOIN

TIME (HR)	TEST TREATMENT A1		TEST TREATMENT A2		REFERENCE TREATMENT B1		REFERENCE TREATMENT B2		RATIO $\left(\frac{\text{Average A}}{\text{Average B}}\right)\%$
0	0.000	(0.0)	0.000	(0.0)	0.000	(0.0)	0.000	(0.0)	N/A
0.5	851.820	(44.9)	821.111	(40.5)	584.960	(30.2)	586.845	(34.9)	142.8
1	1450.852	(31.3)	1615.837	(33.1)	1128.445	(35.4)	1119.066	(25.0)	136.4
1.5	1827.771	(34.2)	1990.566	(23.1)	1449.305	(30.0)	1457.250	(27.2)	131.4
2	2027.793	(32.3)	2302.941	(29.4)	1745.733	(33.2)	1708.092	(22.5)	125.4
2.5	2159.486	(27.6)	2393.936	(31.2)	1926.923	(37.0)	1946.790	(42.7)	117.5
3	2246.057	(37.7)	2297.315	(22.4)	1902.076	(32.9)	1836.248	(26.3)	121.5
4	2218.725	(22.7)	2434.792	(32.5)	1897.952	(28.3)	2178.200	(33.8)	114.2
5	2072.650	(18.6)	2246.886	(26.8)	1838.170	(28.6)	1952.343	(28.5)	114.0
6	1896.186	(18.2)	2157.283	(26.3)	1810.317	(28.5)	1886.630	(22.2)	109.6
7	1885.070	(17.5)	2060.322	(25.5)	1867.669	(23.9)	1812.712	(23.2)	107.2
8	1842.642	(18.4)	1893.702	(23.8)	1711.905	(25.0)	1815.980	(24.6)	105.9
12	1543.560	(24.6)	1573.619	(25.3)	1516.102	(25.8)	1581.518	(23.8)	100.6
16	1302.759	(29.4)	1371.979	(26.1)	1368.588	(29.9)	1399.359	(28.5)	96.6
24	975.830	(45.0)	1024.803	(42.5)	1065.642	(38.1)	1110.388	(34.7)	91.9
36	588.634	(73.2)	618.913	(69.4)	615.872	(66.1)	657.384	(60.7)	94.8
48	335.615	(104.1)	351.004	(103.8)	366.168	(95.7)	377.667	(94.8)	92.3
72	155.924	(204.2)	150.803	(204.0)	157.856	(228.5)	150.627	(189.3)	99.4
96	79.120	(320.3)	72.660	(314.1)	75.083	(355.6)	69.302	(320.2)	105.1

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 ON ORIGINAL

FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #980090
LEAST-SQUARES MEANS FOR PHARMACOKINETIC PARAMETERS
PHENYTOIN
(N=24)¹

	ln AUC 0-t ² (ng·h/mL)	ln AUCinf ² (ng·h/mL)	ln Cmax ² (ng/mL)	tmax (h)	Half-life (h)	kel (1/h)
Morton Grove (A)						
Mean	55986.94	58468.79	2609.7485	3.531	15.458	0.05627
CV%	41.7	49.7	27.9	44.3	84.5	33.6
n	48	48	48	48	48	48
Parke-Davis(B)						
Mean	55821.04	58223.75	2268.0178	5.003	14.924	0.05870
CV%	41.2	50.1	31.4	67.2	94.8	32.0
n	48	48	48	48	48	48
Least-Squares Means						
Morton Grove (A)	55811.53	58218.96	2614.4092			
Parke-Davis(B)	55996.47	58473.60	2263.9746			
Ratio of						
Least-Squares Means						
(A/B)%	99.7	99.6	115.5			
90% Confidence Intervals						
(A/B)%						
Lower limit:	97.3	97.0	107.8			
Upper limit:	102.1	102.2	123.6			
p-Value (ANOVA)						
A vs B	0.8170	0.7759	0.0015			
Period	0.0001	0.0005	0.2091			
Sequence	0.1607	0.1460	0.1331			
Intrasubject CV%	6.6	7.1	19.0			

¹ N is the number of subjects and n is the number of observations

² For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.

Ingredient	Function	Label Claim Quantity per 5 mL	Quantity per Exhibition Batch	Quantity per Production Batch				
Purified Water								
Magnesium Aluminum Silicate, NF								
Glycerin, USP								
Carboxymethylcellulose Sodium, USP								
Purified Water								
Citric Acid Anhydrous, USP								
Sodium Citrate Dihydrate, USP								
Purified Water, USP								
Sodium Benzoate, NF								
Liquid Sugar								
Polysorbate 40, NF								
Phenytoin, USP					Active	125 mg		
Purified Water								
Purified Water								
FD&C Yellow No. 6								
Orange Flavor								
Dehydrated Alcohol, USP								
Vanillin, NF								
Purified Water, USP								
10% Sodium Citrate Solution								
10% Citric Acid Solution								
Purified Water, USP								

¹Volume is converted to weight by multiplying with the specific gravity of Dehydrated Alcohol, USP

²For the exhibition batch, lot #A0253, no Purified Water, USP was used.

³For the exhibition batch, lot # A0253, no pH adjustment was needed.

⁴For the exhibition batch, lot #A0253. of Purified Water, USP were used.

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

40-420

CORRESPONDENCE

ORIGINAL



Regulatory Affairs
Morton Grove Pharmaceuticals, Inc.
6451 West Main Street
Morton Grove, Illinois 60053

Phone (847) 967-5600
Fax (847) 583-5052

September 29, 2000

Via Federal Express

Gary J. Buehler, Acting Director
Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, MD 20857-2773

Re: Original ANDA for Phenytoin Oral Suspension, USP 125 mg/5 mL
(MGP Product Code 8131)

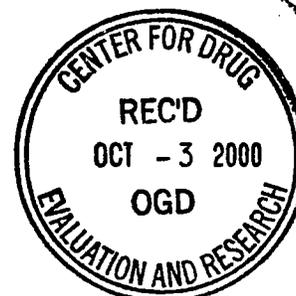
Dear Mr. Buehler,

In accordance with Section 505(j) of the Federal Food, Drug and Cosmetic Act, Morton Grove Pharmaceuticals, Inc., (MGP) has today submitted by courier an original Abbreviated New Drug Application (ANDA) seeking approval to market **Phenytoin Oral Suspension, USP 125 mg/5 mL** that is bioequivalent to the reference listed drug, Dilantin-125[®] manufactured by Parke-Davis, pursuant to NDA #008762.

Morton Grove Pharmaceuticals, Inc., is requesting permission to manufacture **Phenytoin Oral Suspension, USP 125 mg/5 mL** in batches with an expiration dating period of 24 months from the date of manufacture in the container/closure systems listed in this application.

This application includes CMC and BA/BE electronic submissions. We are enclosing electronic diskette (ASCII format), containing the concentration and pharmacokinetic data files for the subject bioavailability study (fda.1.). We are also enclosing herewith the electronic BA/BE submission consisting of 2 diskettes, containing the clinical, pharmacokinetic and analytical ESD files, data files, and companion document in the format required by the FDA for electronic submissions. The electronic CMC submission will be forwarded to the Agency as a new correspondence within 30 days.

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ORIGINAL

Gary J. Buehler, Director
September 29, 2000
Page 2

This ANDA consists of six (6) volumes. As required under 21 CFR 314.94, MGP is filing three copies of this application:

- an archival copy (in blue folders) of the ANDA that contains all the information required for an ANDA,
- a technical review copy (in red folders) which contains all the information in the archival copy, with the exception of the Bioequivalence Section (VI),
- a separate technical review copy of the Bioequivalence Section (VI) (in orange folders), and
- concurrently with the filing of this ANDA, a true copy of the technical sections of the ANDA (including a copy of the 356h form and a certification that the contents are a true copy of those filed with the Office of Generic Drugs) is being sent to the Chicago District Office. This "field copy" is contained in burgundy folders.

We are also enclosing on pages 000003 to 000004 copy of the letter forwarded to Mr. Raymond V. Mlecko, Director, Chicago District Office, FDA.

All materials stamped 'confidential' are considered proprietary information and should not be released under the Freedom of Information Act.

Morton Grove Pharmaceuticals, Inc., commits to resolve any issues identified in the methods validation process after approval.

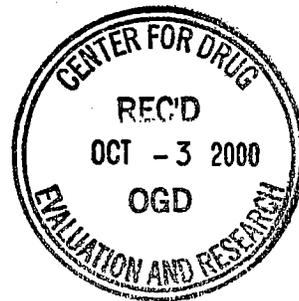
For more detailed information on the organization of this ANDA, please refer to the attached Executive Summary, 'Organization of the ANDA'. Please direct any communications regarding this ANDA to me at the above address. If you need to call or fax me, the numbers are (847) 967-5600 (phone) and (847) 583-5052 (fax).

Thank you for your prompt handling of this submission.

Sincerely,



Yogita Desai, Director
Regulatory Affairs



Encl.

000002



40-420

mef RS



ORIGINAL

October 26, 2000

Regulatory Affairs
Morton Grove Pharmaceuticals, Inc.
6451 West Main Street
Morton Grove, Illinois 60053
Phone (847) 967-5600
Fax (847) 583-5052

Via Federal Express

NEW CORRESP
NC

Gary J. Buehler, Acting Director
Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room 150
Metro Park North
7500 Standish Place
Rockville, MD 20855

Re: CMC Electronic Submission for Phenytoin Oral Suspension, USP 125 mg/5 mL
(MGP Product Code 8131)

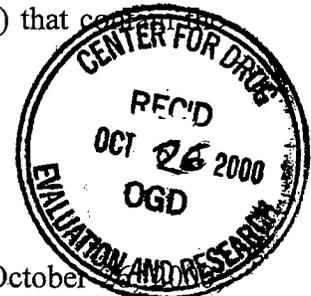
Dear Mr. Buehler:

Morton Grove Pharmaceuticals, Inc., (MGP) hereby submits the CMC Electronic Submission for **Phenytoin Oral Suspension, USP 125 mg/5 mL**. The subject diskette is enclosed.

The original Abbreviated New Drug Application (ANDA) seeking approval to market **Phenytoin Oral Suspension, USP 125 mg/5 mL**, was submitted to the FDA on September 29, 2000. The BA/BE Electronic Submission was forwarded on September 29, 2000. Copies of cover letters of the original application and the BA/BE electronic submission are also enclosed.

This CMC Electronic Submission consists of 1 diskette (archival copy) that contains the following files:

CMC Electronic Submission Document	MGP0002.003
CMC Companion Document	MGP0002.004
CMC EVA Log File	MGP0002.lgc



The information contained in this CMC electronic submission dated October 26, 2000 for **Phenytoin Oral Suspension, USP 125 mg/5 mL**, is not different from the information contained in the hard copy submission dated September 29, 2000 for **Phenytoin Oral Suspension, USP 125 mg/5 mL**, except for the Tables noted in the companion document.

000001

Gary J. Buehler, Acting Director
October 26, 2000
Page 2

MGP acknowledges that:

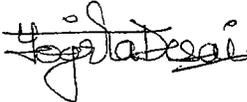
- formatting restrictions may change the appearance of information.
- the archive submission is complete while the ESD/Companion Document is not.
- typographical errors are handled as they are currently handled.

Notification regarding the CMC Electronic Submission has been sent to Mr. Raymond Mlecko, Director, Chicago District Office, FDA (copy enclosed).

Please direct any communications regarding this CMC Electronic Submission to me at the above address. If you need to call or fax me, the numbers are (847) 967-5600 (phone) and (847) 583-5052 (fax).

Thank you for your prompt handling of this submission.

Sincerely,



Yogita Desai
Director, Regulatory Affairs

Enclosures

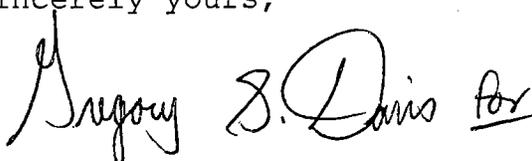
000002



Upon receipt of this communication, you may either amend your application to correct the deficiencies or withdraw your application under 21 CFR 314.99. If you have any questions please call:

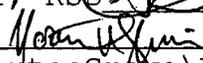
Martin Shimer
Project Manager
(301) 827-5862

Sincerely yours,



Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 40420
DUP/Jacket
Division File
HFD-92
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-615/Mbennett

Endorsement: HFD-615/NMahmud, Chief, RSB  date 27-Nov-20
HFD-615/MShimer, CSO  date 11/27/00
Word File V:\Firmam\MortonGrove\Ltrs&rev.40420rtf
F/T File
ANDA Refuse to Receive!



February 02, 2001

Via Federal Express

Gary J. Buehler, Acting Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Room 150
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Regulatory Affairs
Morton Grove Pharmaceuticals, Inc.
6451 West Main Street
Morton Grove, Illinois 60053

Phone (847) 967-5600
Fax (847) 583-5052

505 (A) OK
J
FEB-2001
Gregory B. Desai

ORIGINAL

ORIG AMENDMENT

N/A/C

RE: ANDA # 40-420, Phenytoin Oral Suspension 125 mg/5 mL
MGP Product Code 8131
Amendment in Response to Refusal to File Letter, Rickman to Desai,
dated December 6, 2000

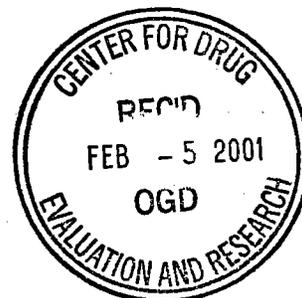
Dear Mr. Buehler:

Pursuant to Peter Rickman's letter of December 6, 2000 (copy enclosed), Morton Grove Pharmaceuticals, Inc. (MGP) hereby amends the original ANDA #40-420, **Phenytoin Oral Suspension 125 mg/5 mL**. A complete copy of this amendment is being sent to Raymond V. Mlecko, Director, Chicago District Office, FDA. For your convenience, our responses are preceded by your comments.

If you have any further questions, please call me at (847) 967-5600.

Sincerely,

AniMa Katragadda
for Yogita Desai,
Director, Regulatory Affairs



000001



ORIGINAL

July 20, 2001

Regulatory Affairs
Morton Grove Pharmaceuticals, Inc.
6451 West Main Street
Morton Grove, Illinois 60053
Phone (847) 967-5600
Fax (847) 583-5052

Via Airborne Express

Gary J. Buehler, Acting Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Room 150
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

RECEIVED

ORIG. AMENDMENT
N/AB

RE: **ANDA # 40-420, Phenytoin Oral Suspension, USP 125 mg/5 mL**
MGP Product Code 8131
Bioequivalency Amendment in Response to Deficiency Letter,
Conner, FDA to Desai, MGP dated June 20, 2001

Dear Mr. Buehler:

The sponsor, Morton Grove Pharmaceuticals, Inc. (MGP), is providing this amendment to address the bioequivalency comments identified in the letter dated June 20, 2001 (copy enclosed) for ANDA # 40-420, Phenytoin Oral Suspension, USP 125 mg/5 mL. A complete copy of the amendment was sent to Raymond V. Mlecko, Director, Chicago District Office, FDA.

For your convenience, our responses are preceded by your comments.

If you have any questions, please call me at 847-967-5600.

Thank you for your attention to this matter.

Sincerely,

Yogita Desai
Regulatory Affairs



Encl.

000001



September 20, 2001

Regulatory Affairs
Morton Grove Pharmaceuticals, Inc.
6451 West Main Street
Morton Grove, Illinois 60053
Phone (847) 967-5600
Fax (847) 583-5052

Via Airborne Express

Gary J. Buehler, Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Room 150
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

ORIGINAL

ORIG AMENDMENT
N/A M

**RE: ANDA # 40-420, Phenytoin Oral Suspension, USP 125 mg/5 mL
(MGP Product Code 8131)
Minor Amendment in Response to Chemistry Deficiency Letter,
Fang, FDA to Desai, MGP dated April 27, 2001**

Dear Mr. Buehler:

The sponsor, Morton Grove Pharmaceuticals, Inc. (MGP), is providing this amendment to address the chemistry comments identified in the letter dated April 27, 2001 (copy enclosed). This letter included both CMC and Bioequivalency comments. Responses for the Bioequivalency comments were submitted to the Agency on July 20, 2001.

A complete copy of this amendment is being sent to Raymond V. Mlecko, Director, Chicago District Office, FDA.

For your convenience, our responses are preceded by your comments.

If you have any questions, please call me at 847-967-5600.

Thank you for your attention to this matter.

Sincerely,

Yogita Desai
Regulatory Affairs



Encl.

000001

*MP
9/25/01*

ORIGINAL



February 22, 2002

Regulatory Affairs
Morton Grove Pharmaceuticals, Inc.
6451 West Main Street
Morton Grove, Illinois 60053
Phone (847) 967-5600
Fax (847) 583-5052

Via Federal Express

Mr. Gary J. Buehler, Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Room 150
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

N/mm
ORIG AMENDMENT

*Noted.
To
Yanping
M Anderson
2/28/02*

**RE: ANDA # 40-420, Phenytoin Oral Suspension, USP 125 mg/5 mL
(MGP Product Code: 8131)**

- **Minor Amendment in Response to Deficiency Letter from Fang, FDA to Desai, MGP dated November 13, 2001**
- **Other CMC Revision**

Dear Mr. Buehler:

The sponsor, Morton Grove Pharmaceuticals, Inc. (MGP), is providing this amendment to address the chemistry comments identified in the letter from Fang, FDA, to Desai, MGP, dated November 13, 2001 (copy enclosed) and notify of other CMC revision.

A complete copy of this amendment is being sent to Mr. Arlyn H. Baumgarten, Acting Director, Chicago District Office, FDA.

For your convenience, our responses are preceded by your comments.

If you have any questions, please call me at 847-967-5600.

Thank you for your attention to this matter.

Sincerely,

Yogita Desai
Regulatory Affairs



Encl.

000001

*MW
2/26/02*